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TOPIC HIGHLIGHT

2016 Inflammatory Bowel Disease: Global view

Role of antibiotics for treatment of inflammatory bowel disease

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Abstract

Inflammatory bowel disease is thought to be caused by an aberrant immune response to gut bacteria in a genetically susceptible host. The gut microbiota plays an important role in the pathogenesis and complications of the two main inflammatory bowel diseases: Crohn's disease (CD) and ulcerative colitis. Alterations in gut microbiota, and specifically reduced intestinal microbial diversity, have been found to be associated with chronic gut inflammation in these disorders. Specific bacterial pathogens, such as virulent *Escherichia coli* strains, Bacteroides spp, and *Mycobacterium avium* subspecies paratuberculosis, have been linked to the pathogenesis of inflammatory bowel disease. Antibiotics may influence the course of these diseases by decreasing concentrations of bacteria in the gut lumen and altering the composition of intestinal microbiota. Different antibiotics, including ciprofloxacin, metronidazole, the combination of both, rifaximin, and anti-tuberculous regimens have been evaluated in clinical trials for the treatment of inflammatory bowel disease. For the treatment of active luminal CD, antibiotics may have a modest effect in decreasing disease activity and achieving remission, and are more effective in patients with disease involving the colon. Rifamixin, a non absorbable rifamycin has shown promising results. Treatment of suppurative complications of CD such as abscesses and fistulas, includes drainage and antibiotic therapy, most often ciprofloxacin, metronidazole, or a combination of both. Antibiotics might also play a role in maintenance of remission and prevention of post operative recurrence of CD. Data is more sparse for ulcerative colitis, and mostly consists of small trials evaluating ciprofloxacin, metronidazole and rifaximin. Most trials did not show a benefit for the treatment of active ulcerative colitis with antibiotics, though

2 meta-analyses concluded that antibiotic therapy is associated with a modest improvement in clinical symptoms. Antibiotics show a clinical benefit when used for the treatment of pouchitis. The downsides of antibiotic treatment, especially with recurrent or prolonged courses such as used in inflammatory bowel disease, are significant side effects that often cause intolerance to treatment, *Clostridium dificile* infection, and increasing antibiotic resistance. More studies are needed to define the exact role of antibiotics in inflammatory bowel diseases.

Key words: Antibiotic treatment; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease

Core tip: The gut microbiota plays an important role in the pathogenesis and complications of inflammatory bowel disease. Antibiotics may influence the course of inflammatory bowel disease by decreasing concentrations of bacteria in the gut lumen and altering the composition of intestinal microbiota. In Crohn's disease, antibiotics may have a modest effect in decreasing disease activity and achieving remission, are more effective in patients with disease involving the colon, and are useful in the treatment of suppurative complications. Data is more sparse and less conclusive for the treatment of ulcerative colitis, though there might be some benefit in antibiotic treatment. Side effects, the risk of *Clostridium dificile* infection, and increasing antibiotic resistance should be considered. Further studies are needed to define the role of antibiotic treatment in inflammatory bowel diseases.

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INTRODUCTION

Inflammatory bowel disease (IBD) is an immune mediated relapsing idiopathic intestinal condition. Ulcerative colitis (UC) and Crohn's disease (CD) compromise the two major types of IBD. UC is a chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited to the mucosal layer of the colon, and is characterized by bloody stools and irregular crypt architecture. CD is characterized by transmural involvement, skip lesions, and granulomas that can affect the entire gastrointestinal tract and causes fibrosis, intestinal obstruction, and fistulae[1]. The incidence of IBD varies within different geographic regions, with a prevalence of UC of 500 per 100000 individuals in Europe and 250 per 100000 in North America and for CD: 320 per 100000 in Europe and 200 per 100000 in the United States[2]. The incidence of IBD is rising with time, and may emerge as a global disease[3].

The etiology of IBD has not been clearly elucidated. An aberrant immune response to gut bacteria in a genetically susceptible host is considered to be the basis of this disorder with dysregulation of the innate and adaptive mucosal immune system directed against luminal bacteria or their products in the intestinal lumen[4,5].

GUT MICROBIOTA AND IBD

The adult gut ecosystem contains trillions of organisms from over 1000 species, with the most abundant species being from the *Firmicutes* and *Bacteroidetes* phyla[6]. Changes in gut bacterial population occur over time, and depend on age, diet, hygiene, climate, geography and ethnicity[7,8]. Nowadays over 25 diseases or syndromes have been linked to an altered intestinal microbiome[9]. There is abundant data confirming the importance of gut microbiota in the inflammatory process that exists in IBD[10,11]. For example, genetically engineered mice deficient in the cytokines IL-2 and IL-10 or rats containing the HLA-B27 transgene (genetic mutations that have been linked to IBD) are protected from colitis in the germ-free state, but develop IBD upon reconstitution of normal gut flora, thus implying that colitis depends on the presence of gut bacteria[12,13].

The specific bacteria that trigger an aberrant immune response and thereby contribute in the pathogenesis of IBD have not yet been found. *Mycobacterium avium* subspecies paratuberculosis (MAP) has long been debated as a cause of CD[14]. A meta-analysis from 2007 concluded that the association of MAP with CD seems to be specific (OR of 7.01, compared to patients without IBD and 4.13, compared to patients with UC, when assessed by PCR), but its role in the etiology of CD remains to be defined[15]. Other bacteria that have been reported to be involved in the development of CD are *Yersinia enterocolitica* and *Listeria monocytogenes*[16]. Alterations in gut microbiota, and specifically reduced intestinal microbial diversity, have been found to be associated with chronic gut inflammation in IBD[10,17]. Patients with IBD have a reduced abundance of Eubacterium spp, Lactobacillus spp, and Bacteroides spp[17]. It has been hypothesized that loss of bacteria converting non digestible dietary fiber into short chain fatty acids may contribute to development of IBD[18]. UC and CD patients have different fecal bacterial composition[19]. In patients with IBD there is a relative increase in gut Proteobacteria, mainly due to a higher abundance of adherent invasive *Escherichia coli* (AIEC), which is more often found in patients with ileal CD[10,20]. These bacteria invade the intestinal epithelium and replicate in enterocytes with impaired expression of immune

associated molecules that are found in CD, thus causing gut inflammation[21]. Other bacteria, such as *Faecalibacterium prausnitzii*, which is decreased in patients with IBD, were found to protect mice from inflammatory colitis[10,22]. Not only the composition, but also the function of the gut microbiota seems to differ in people with CD, which have higher levels of fecal trypsin, an enzyme that is produced by the pancreas and is normally inactivated by Bacteroides spp[23].

There is also ongoing debate whether mucosa attached bacteria play a more important role than luminal bacteria in the propagation of IBD[10]. Mucosal surfaces of IBD patients were found to be densely colonized with *Bacteroides fragilis*[24].

RATIONALE FOR USING ANTIBIOTICS IN THE TREATMENT OF IBD

Pros

Since intestinal bacteria play an important role in the development of IBD, modulation of the gut microbiota has become an active area of research. Manipulating the gut microbiota can be achieved by prebiotics, probiotics, fecal transplants, and antibiotics[6,11,25]. Prebiotics are dietary compounds that cause specific changes in the composition and/or activity of the gastrointestinal microbiota, and probiotics are live organisms, which when administered in adequate amounts confer a health benefit on the host.

Antibiotics may influence the course of IBD by decreasing concentrations of bacteria in the gut lumen and altering the composition of intestinal microbiota to favor beneficial bacteria[11,25]. They can also target specific bacteria that are hypothesized to be implicated in the pathogenesis of IBD such as administration of ciprofloxacin, aminoglycosides or rifaximin against virulent *Escherichia coli* and other gram negative enteric bacteria, metronidazole for anaerobes (specifically *Bacteroides fragilis*), or anti tuberculous drugs designed to treat mycobacterial infection (MAP), which has been hypothesized to have a role in the development of CD[26].

Antibiotics can be used for treating the primary disease process of IBD (including luminal disease and fistulizing disease for CD and colitis in the case of UC), for treating bacterial overgrowth, or for treating septic complications of IBD, such as abscesses and post operative wound infections. It may also be used to maintain remissions, or for the treatment of pouchitis.

Cons

Antibiotic treatment can be associated with negative outcomes as well. Side effects of ciprofloxacin include tendonitis, tendon rupture, photosensitivity, inhibition of cartilage growth in fetuses and children, oral thrush, and QT prolongation[27,28]. Metronidazole frequently causes gastrointestinal (GI) disturbances and may cause permanent peripheral neuropathy if used for prolonged time intervals[29]. *Clostridium dificille* infection (CDI) is also an important caveat of all antibiotic treatments. Patients with IBD are at increased risk of developing CDI and have worse outcomes of CDI[30,31]. Recently, concerns that antibiotics may elicit IBD by altering the gut microbiota, have been raised and some studies found a link between antibiotics and CD[32]. The largest study showed a strong association between CD and prior antibiotic use in 577627 Danish children, suggesting that early life changes in intestinal microbiota may influence the development of the gut immune system[33]. Antibiotics may also cause a rebound effect on gut bacteria, after cessation of therapy, as demonstrated in a study of 20 patients with IBD that found a dramatic increase in concentrations of mucosal bacteria as soon as 1 wk after cessation of antibiotic therapy, remaining at a level that is at least one power higher over a period of 5 mo as compared to patients without antibiotic treatment[34]. Another caveat of antibiotic treatment is the development of antibiotic resistance. A Chinese study from 2014 found that two thirds of gram negative isolates from abdominal abscess isolates in patients with CD were resistant to ciprofloxacin[35]. Another study demonstrated rifaximin resistance in 12/48 IBD associated ileal *Escherichia coli* strains, that was significantly associated with prior rifaximin treatment and was found to be correlated with a specific mutation in bacterial efflux pump[36].

ANTIBIOTIC TREATMENT FOR CD

The greatest number of clinical studies concerning antibiotic treatment for IBD has been conducted on patients with CD. Antibiotics can be used to treat primary active disease including: luminal disease and fistulizing disease, and they may be used for secondary septic complications such as abscesses, post operative infections or even for the maintenance of remission. Different antibiotics have been evaluated in clinical trials, most often ciprofloxacin, metronidazole (each by itself and in combination), rifaximin, clarithromycin and anti-tuberculous regimens.

Active luminal disease

Several meta-analyses have been published concerning antibiotic treatment in patients with active CD. A meta-analysis from 2011, found antibiotics to be superior to placebo for the induction of remission of active CD (RR for disease remission 0.85, 95%CI: 0.73-0.99)[37]. A meta analysis from 2012 included 11 randomized, double blind studies involving a total of 832 patients with CD that were treated with broad spectrum antibiotics, including ciprofloxacin, metronidazole, combination of both, rifaximin, clarithromycin, and others. Treatment duration varied from 2-16 wk. Some

patients received concomitant therapy with steroids or immunosuppressants. Clinical improvement occurred in 56.1% (214/429) of patients in the antibiotic group and 37.9% (153/403) of patients in the placebo group. The OR for clinical improvement was 1.35 (95%CI: 1.16-1.58)[38]. Another meta-analysis that was recently published included 15 randomized control trials, with 1407 patients with CD. The antibiotics used included ciprofloxacin, clarithromycin, metronidazole and rifaximin and treatment duration was at least 4 wk. The combined RR for clinical remission or response in patients with CD was 1.33 (95%CI: 1.17-1.51, $P < 0.00001$)[39].

Analysis of the studies evaluating ciprofloxacin monotherapy found no significant difference in the clinical response rate between the patients treated with ciprofloxacin and those treated with placebo[39]. Although a single trial of 47 patients with moderately active resistant disease who were randomly assigned to receive ciprofloxacin 500 mg, orally twice daily for 6 mo had significantly lower disease activity scores than those who received placebo[40]. Treatment duration of 4-10 wk was associated with a significant improvement in outcomes, but in trials where patients received > 10 wk of antibiotic treatment no significant difference was found[39]. This might be due to development of antibiotic resistance after prolonged exposure of intestinal flora to ciprofloxacin. Ciprofloxacin treatment for active CD was found to be more effective in patients with colonic involvement, a consistent finding in studies of other antibiotic treatments as well[41].

Analysis of trials evaluating metronidazole shows a modest benefit in treatment of active CD. The largest randomized controlled trial (RCT) included 105 patients (though only 56 completed the study) who received either metronidazole for 16 wk or placebo. There was a significant decrease in disease activity index, but no difference in remission rates[42]. Patients receiving metronidazole 20 mg/kg per day had a greater improvement in disease activity than those receiving 10 mg/kg per day. Metronidazole was more effective in patients with disease involving the colon[42]. The incidence of side effects reported in trials using metronidazole varies from 10%-50%, according to dose and length of therapy, with the most frequent side effects being GI intolerance, neurotoxicity and metallic taste[43]. Up to one third of patients cease therapy due to intolerance[44].

Combination therapy with ciprofloxacin and metronidazole was evaluated in a few trials. One study, including 134 patients that received metronidazole 500 mg twice daily and ciprofloxacin 500 mg twice daily or placebo for 8 wk (all patients received concurrent budesonide) found no difference in remission rates, though in patients with colonic involvement, more patients in the antibiotics group achieved remission (did not achieve statistical significance)[41]. Another study of patients assigned to ciprofloxacin and metronidazole *vs* methylprednisolone for 12 wk found a larger proportion of patients in clinical remission in the steroid group (did not achieve statistical significance)[45].

Rifaximin, which is a minimally absorbed broad spectrum antibiotic with gram positive, gram negative and anaerobic coverage, was assessed in a few clinical trials[46]. A meta-analysis from 2011, included 2 trials of treatment with rifaximin for active CD. These trials involved 485 patients and suggested that rifamixin was effective at inducing remission, with a decreased risk of persistence of active disease (RR = 0.81, 95%CI: 0.68-0.97) in patients that received rifaximin *vs* placebo[37]. All doses were combined for this meta-analysis although the data suggested 800 mg bid was more effective than either 400 mg bid or 1.2 g bid for 12 wk. Another study of 402 patients with CD, found that in patients that received 12-wk of treatment with extended release rifaximin, at the end of the study period: 62% of patients who received the 800-mg dosage of rifaximin were in remission, compared with 43% of patients who received placebo (43 of 101) ($P = 0.005$)[47]. Remission was achieved by 54% and 47% of the patients given the 400-mg and 1200-mg dosages of rifaximin-extended release, respectively; these rates did not differ from those of placebo. The lack of a dose response relationship was probably caused by the higher number of patients that discontinued therapy in the 1200 mg group. Again, colonic involvement was associated with a higher response to antibiotic treatment[47]. Another trial of rifaximin 800 mg twice daily for 12 wk compared with placebo, found that 100% of patients in the rifaximin group achieved remission compared to 84% in the placebo group[48].

Therapy directed at atypical mycobacteria was evaluated in several clinical trials. A meta-analysis published in 2000 of 8 clinical studies that evaluated anti mycobacterial therapy for active CD (each trial used a different combination of drugs), found that only in the 3 trials where concomitant steroid therapy was used, there was a positive effect of this treatment and concluded that treatment of CD with antimycobacterial therapy does not seem to be effective without a course of corticosteroids to induce remission[49]. A large trial from 2007 included 213 patients that were randomly assigned to receive a combination of clarithromycin, rifabutin and clofazimine or placebo for 2 years, in addition to 16 wk of prednisolone. The only time interval where a significant effect was noted was at 16 wk (when concomitant steroids were still given). Mucosal levels of MAP were not measured before and after therapy, thus it is not clear if improvement in symptoms was associated with a decrease in MAP[50].

Suppurative complications: Abscesses and fistulas

Most of the studies mentioned above were conducted on patients with active luminal disease. Perforating, suppurative complications of CD, such as intra-

abdominal/anorectal abscesses and fistulas, are linked to transmural translocation of bacteria from the diseased bowel to contiguous tissue[51]. These complications are common in patients with CD, as occurrence rates for intraabdominal abscesses vary from 10% to 30%[52] in the literature and anorectal fistulas develop in approximately 20% to 30% of patients with CD[53]. Few studies of antibiotic treatment have been directed at patients with fistulizing disease. In the meta-analysis published in 2015, a subgroup analysis of three trials where ciprofloxacin was used to treat perianal fistulas, revealed a significant increase in clinical response and remission in the ciprofloxacin group *vs* the placebo group (RR = 1.64, 95%CI: 1.16-2.32, P = 0.005)[39]. One of the trials included 25 patients that were randomized to ciprofloxacin, metronidazole, or placebo. Remission at week 10 occurred in 30% treated with ciprofloxacin, no patients treated with metronidazole, and 1 patient (12.5%) treated with placebo (P = 0.41). Response at week 10 occurred in 4 patients (40%) treated with ciprofloxacin, 1 patient (14.3%) treated with metronidazole, and 1 patient (12.5%) treated with placebo (P = 0.43)[54]. There are no other controlled trials, but clinical reports observed that long term antibiotics are needed to prevent recurrence of fistulas. In a study of 21 patients with chronic unremitting perineal CD that received metronidazole for a mean of 6.5 mo, drainage, erythema, and induration diminished dramatically in all patients, and complete healing was obtained in 10 of 18 patients maintained on therapy, though 50% of patients developed neurologic side effects requiring dose reduction or discontinuation[55].

Treatment of abdominal and anorectal abscesses consists of surgical or percutaneous drainage combined with antibiotic therapy. Small (< 3 cm) abscesses can be treated with antibiotics alone, especially in cases without associated fistulas or in immunomodulator-naive patients. Antibiotics should cover gram negative bacteria and anaerobes. A combination of fluoroquinolones or cephalosporins and metronidazole is considered appropriate[51].

Maintenance of remission

Recurrence of active disease is common after remission is achieved in patients with CD. Long term treatment with antibiotics might decrease recurrence rate, though it is frequently associated with side effects and intolerance to treatment. A meta-analysis that included 3 RCTs treating 186 patients with quiescent CD found a statistically significant effect of antibiotics in preventing CD relapse compared with placebo (RR of relapse = 0.62; 95%CI: 0.46-0.84)[37]. All studies evaluated antimicrobials that could be considered antimycobacterial although all studied different regimens. Follow-up was for 9-12 mo, and all trials did not report method of randomization or method of concealment of allocation and so had unclear risk of bias. A study of 83 patients with CD that achieved remission with standard therapy of prednisone and budesonide, evaluated 800 mg of rifaximin twice daily for 12 wk *vs* placebo, and found that at 12 wk 100% were still in remission in the rifaximin arm *vs* 84% in the placebo arm. Superiority in maintenance of remission was demonstrated at 24 wk (78% *vs* 41%), and at 48 wk 55% *vs* 25% as well[48].

Prevention of post operative recurrence

Endoscopic and clinical recurrence of CD is a common occurrence after surgical resection[56,57]. Luminal bacteria might play a potential role in increasing the likelihood of recurrence, as one study found that recurrent disease developed only when the mucosa was re-exposed to luminal contents[58]. Prevention of post operative recurrence of CD with antibiotics was assessed in a few clinical trials[59]. One trial showed that the combination of metronidazole (for one month) and azathioprine (for one year) was associated with lower recurrence rates than receiving metronidazole alone[60]. Other studies found that metronidazole, compared to placebo, decreases the recurrence of CD post operatively[61].

Bacterial overgrowth

Bacterial overgrowth, which is relatively common in CD, causes symptoms varying from mild GI discomfort to severe diarrhea and malabsorption[62]. Several antibiotic regimens, including ciprofloxacin, metronidazole and rifaximin are effective in normalizing hydrogen breath tests, which is one of the non invasive methods for diagnosing small intestinal bacterial overgrowth[63,64]. In a study from 2000, 14 patients with inactive CD of the ileum and bacterial overgrowth, as assessed by a hydrogen breath test, were blindly allocated to receive rifaximin (1200 mg/d) or placebo for one week. After 14 d, the hydrogen breath test proved to be negative in seven out of seven patients treated with rifaximin, and in two out of seven in the placebo group. After 30 d, the hydrogen breath test was positive in all patients of the rifaximin and placebo group, suggesting that rifaximin only transiently clears bacterial overgrowth in patients with CD[65].

ANTIBIOTIC TREATMENT FOR UC

There is less data concerning treatment of UC with antibiotics, consisting of trials with small numbers of patients, with a lack of well designed, placebo controlled trials. Several different antibiotics, alone or in combination have been evaluated for the treatment of UC.

Active UC

A prospective RCT, of oral metronidazole 1.35 g/d compared to sulfasalazine 4.5 g/d for 28 d for the outpatient management of 46 patients with mild-

moderate UC, found that 6/23 (26%) receiving metronidazole improved *vs* 13/19 patients receiving sulfasalazine (68%) ($P < 0.01$), concluding that metronidazole is ineffective in the therapy of an acute attack of non severe UC[66]. Another RCT evaluated 39 patients with severe UC, treated with metronidazole or placebo in adjunct to steroids for 5 d, found no significant difference between the 2 groups[67]. Two RCTs comparing intravenous or oral therapy in adjunct to steroids for mild-severe UC, for 2 wk, found no significant difference in clinical improvement[68,69]. In Another study 39 patients with severe UC received either metronidazole (0.5 g tid) and tobramycin (4 mg/kg tid) or placebo ($n = 20$) in addition to total parenteral nutrition, intravenous hydrocortisone (100 mg qid) and hydrocortisone enemas (100 mg bid). Sixty three percent of patients treated with antibiotics and 65% with placebo showed substantial improvement[70]. In another double-blind randomized placebo controlled clinical trial of Ciprofloxacin and probiotic *Escherichia coli* Nissle add-on treatment in 100 patients with active UC, among patients treated with Cipro/placebo, 78% reached remission *vs* 89% in the placebo/placebo group[71].

On the other hand, a trial of 6 mo of ciprofloxacin *vs* placebo in addition to steroids in 83 patients with poor response to conventional therapy, found that treatment failure in the ciprofloxacin group was 21% *vs* 44% in the placebo group[72]. Another study found that in 84 patients with an acute relapse of UC that were randomized to receive oral tobramycin or placebo for 1 wk as an adjunct to steroid therapy, 74% in the tobramycin group achieved complete symptomatic remission compared with 43% in the placebo group ($P = 0.008$). The tobramycin group also achieved better histological scores ($P < 0.05$) at endpoint[73]. A trial of rifaximin for the treatment of active UC found rifaximin to be superior to placebo[74]. In an open label trial of 94 patients with steroid refractory or dependent active UC that were treated with oral amoxicillin, tetracycline and metronidazole for two weeks, 63.3% of steroid refractory and 73.4% of steroid dependent patients showed a clinical response within 2 wk[75]. A meta-analysis from 2011, included nine trials involving 662 patients with active UC, with only one low risk of bias trial and a finding of high heterogeneity between the trials suggesting publication bias or other small study effects. Therapy was given for 7 d to 3 mo and generally patients with moderately active UC were recruited. There were three trials that evaluated ciprofloxacin with no statistically significant benefit over placebo. All other trials assessed different single or combinations of antibiotics. Overall, there was a statistically significant effect in favor of antibiotics (RR of active UC = 0.64; 95%CI: 0.43- 0.96, $P = 0.03$)[37]. Another meta-analysis from 2012, found that UC patients receiving antibacterial therapy are 2.17 more likely to experience clinical remission[38].

Maintenance of remission

As in CD, persistent intestinal inflammation linked to intestinal dysbiosis is thought to cause exacerbations of UC, thus, theoretically, antibiotics might be used for maintenance of remission. In a double-blind, randomized trial, the effectiveness of metronidazole (0.6 g/d) against sulfasalazine (2 g/d) for 12 mo in the maintenance of remission in patients with UC was assessed. Forty patients entered the trial and 33 completed it. Remission was maintained for 12 mo in 9 out of 20 patients by metronidazole and in 3 of 15 patients by sulfasalazine ($P < 0.05$), which suggests that metronidazole may be useful in the maintenance of remission in patients with UC[76]. Another trial that reported a 2-year follow-up of an acute UC trial that compared 7 d of oral tobramycin *vs* placebo found no difference in relapse rates at 1 and 2 years suggesting 7 d of tobramycin did not influence long-term relapse rates[77].

Pouchitis

Pouchitis is the most frequently observed long-term complication of total proctocolectomy with ileal pouch-anal anastomosis, which is the definitive treatment for UC. The pathogenesis of pouchitis is unclear, but it is hypothesized to result from an abnormal immune response to altered luminal and/or mucosal bacteria, with a gradual shift from an ileum-like to a colon-like bacterial community, in genetically susceptible hosts. Pouchitis is classified as either acute (< 4 wk of symptoms) or chronic ($\geqslant$ 4 wk)[78]. The majority of patients with acute pouchitis respond to initial therapy with antibiotics, but approximately 60% have at least one recurrence[79]. In a 2010 systematic review that included four randomized trials evaluating five agents for treatment of acute pouchitis, ciprofloxacin was more effective at inducing remission as compared with metronidazole. Rifaximin was not found to be more effective than placebo[80]. In patients with chronic pouchitis, a study found that in 15 patients with antibiotic refractory pouchitis, 80% of patients achieved clinical remission with individualized antinmicrobial therapy based on sensitivity test results of coliform bacteria[81].

Maintenance therapy after resolution of pouchitis has also been evaluated. In one study, 51 patients in remission of pouchitis began maintenance therapy with rifaximin 200 mg/d (to 1800 mg/d) for up to 24 mo. Pouchitis Disease Activity Index symptom scores were assessed every 1-3 mo to evaluate efficacy. Sixty-five percentage of them maintained remission through 3 mo[82].

GUIDELINES FOR ANTIBIOTIC TREATMENT FOR IBD

Guidelines of various associations that have been published for the treatment of IBD and consider the role of antibiotic therapy will be reviewed.

CD treatment guidelines

The American College of Gastroenterology (ACOG) guidelines from 2009 state that although antibiotics are widely used in clinical practice for the treatment of CD, controlled trials have not consistently demonstrated efficacy in the setting of luminal disease. Infection or abscess requires appropriate antibiotic therapy or drainage. Non-suppurative perianal complications of CD should be treated with metronidazole alone or in combination with ciprofloxacin, with need for continuous therapy to prevent recurrent drainage[83].

The British Society of Gastroenterology (BSG) published guidelines concerning the treatment of IBD in 2011[84]. They summarize that antibiotics have an important role in treating secondary complications in CD, such as abscesses and bacterial overgrowth, and that there is some evidence that metronidazole and ciprofloxacin might have specific uses in CD.

The European Crohn's and Colitis Organisation (ECCO) guidelines published in 2011 states that the Consensus does not favor antibiotics for moderately active ileal CD as first-line therapy unless septic complications are suspected. For moderate to severe ileocecal disease- antibiotics should be reserved for patients with a temperature or focal tenderness, or in whom imaging has indicated an abscess[85]. Adding ciprofloxacin and metronidazole to budesonide has shown no advantage over budesonide alone in active CD.

The Association of American Family Physicians guidelines for management of CD from 2003 state that in the treatment of mild to moderate active CD, antibiotic therapy with metronidazole, ciprofloxacin or a combination of both, may be an acceptable alternative to other treatments[86].

UC treatment guidelines

The ACOG guidelines for treatment of UC from 2010, do not mention antibiotic treatment for mild-moderate disease[87]. For severe colitis, in the absence of any proven infection, controlled trials of antibiotics have showed no therapeutic benefit from the use of antibiotics when added to intravenous steroids. However, protocols outlining treatment regimens for severe colitis generally include broad-spectrum antibiotics for patients with signs of toxicity, or with worsening symptoms despite maximal medical therapy.

The BSG states in their guidelines that there is no clear-cut evidence to support the use of antibiotics in UC as disease modifying therapy[84].

The ECCO guidelines from 2012 state that antibiotics should be used in the treatment of UC only if infection is considered (such as in an acute, first attack of short duration, or after travel to an area where amoebiasis is endemic), or immediately prior to surgery[88]. Controlled trials of oral or intravenous metronidazole, tobramycin, ciprofloxacin or vancomycin in acute colitis have shown no consistent benefit in addition to conventional therapy.

CONCLUSION

There is an increasing body of evidence that gut microbiota play an important role in the pathogenesis of both CD and UC. For CD patients: treatment with metronidazole, with or without ciprofloxacin and treatment with rifaximin might produce a modest benefit when administered for active luminal diseases, especially involving the colon. Metronidazole, ciprofloxacin or the combination of both are recommended for treatment of perianal fistula and suppurative complications such as abscesses. Antibiotics might play a role for maintenance of remission and prevention of post-operative recurrence. For UC, no consistent benefit was shown for treatment of non-severe colitis, though broad spectrum antibiotics might be helpful in severe or fulminant disease. Antibiotics are important in the treatment of pouchitis. It is important to define the indications for antibiotic treatment in IBD in order to reduce unnecessary treatment that may lead to increased antibiotic resistance of intestinal flora, and in the intention of optimizing treatment. Large sample sized, multi center RCTs are needed in order to better define the role of antibiotic therapy in IBD.

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